Management of patients with acute lymphoblastic leukemia in routine clinical practice: Minimal residual disease testing, treatment patterns and clinical outcomes in Belgium, Greece and Switzerland

Deeren, Dries ; Balabanov, Stefan ; Nickel, Katharina ; Giannopoulou, Christina ; Gonzalez-McQuire, Sebastian ; Kutikova, Lucie ; Bouwmeester, Walter ; Spyridonidis, Alexandros

Abstract: OBJECTIVES To describe real-world management and clinical and economic outcomes of patients with B-cell precursor acute lymphoblastic leukemia (ALL) in Belgium, Greece and Switzerland. METHODS This descriptive, retrospective medical chart review collected patient-level data in 2018 from adults with 1 minimal residual disease (MRD) test during front-line ALL treatment. Data were stratified by MRD status. RESULTS Eighty-two patients were included (median age 44 years, 23 % Philadelphia chromosome-positive; MRD-positive: n = 17, MRD-negative: n = 50, MRD result unknown: n = 15). HyperCVAD (32 %) and HOVON (26 %) were the most frequently used front-line treatment protocols; 22 % of patients received stem cell transplantation. Overall, 76 % of ALL patients were hospitalized (mean 1.1 hospitalization/month). Complete hematological response (CRh) occurred in 66/82 patients (80 %). Median relapse-free survival from CRh was 32.7 months (MRD-positive: 11.7 months; MRD-negative: 33.3 months). Median overall survival from diagnosis was 28.9 months (MRD-positive: 15.3 months; MRD-negative: not reached). Most patients (88 %) were MRD tested during induction; testing rates considerably decreased thereafter (39 % during consolidation). CONCLUSIONS B-cell precursor ALL represents a clinical burden and impacts healthcare resources; MRD-positive patients have worse prognosis than MRD-negative patients. Efforts should be made to adhere to recommendations for MRD testing in clinical guidelines.

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Research paper

Management of patients with acute lymphoblastic leukemia in routine clinical practice: Minimal residual disease testing, treatment patterns and clinical outcomes in Belgium, Greece and Switzerland

Dries Deeren[a,*], Stefan Balabanov[b], Katharina Nickel[c], Christina Giannopoulou[d], Sebastian Gonzalez-McQuire[d], Lucie Kutikova[d], Walter Bouwmeester[e], Alexandros Spyridonidis[f]

[a] AZ Delta, Wilgenstraat 2, B-8800, Roeselare, Belgium
[b] University Hospital of Zurich, Rämistrasse 100, 8091, Zurich, Switzerland
[c] Pharmerit International, Krausenstraße 8, 10117, Berlin, Germany
[d] Amgen (Europe) GmbH, Suurstoffi 22, P.O. Box 94, CH-6343, Rotkreuz, Switzerland
[e] Pharmerit International, Marten Meesweg 107, 3068 AV, Rotterdam, The Netherlands
[f] University of Patras, University Hospital, BMT Unit, 26500, Rio, Greece

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ABSTRACT

Objectives: To describe real-world management and clinical and economic outcomes of patients with B-cell precursor acute lymphoblastic leukemia (ALL) in Belgium, Greece and Switzerland.
Methods: This descriptive, retrospective medical chart review collected patient-level data in 2018 from adults with ≥1 minimal residual disease (MRD) test during front-line ALL treatment. Data were stratified by MRD status.
Results: Eighty-two patients were included (median age 44 years, 23 % Philadelphia chromosome-positive; MRD-positive: n = 17, MRD-negative: n = 50, MRD result unknown: n = 15). HyperCVAD (32 %) and HOVON (26 %) were the most frequently used front-line treatment protocols; 22 % of patients received stem cell transplantation. Overall, 76 % of ALL patients were hospitalized (mean 1.1 hospitalization/month). Complete hematological response (CRh) occurred in 66/82 patients (80 %). Median relapse-free survival from CRh was 32.7 months (MRD-positive: 11.7 months; MRD-negative: 33.3 months). Median overall survival from diagnosis was 28.9 months (MRD-positive: 15.3 months; MRD-negative: not reached). Most patients (88 %) were MRD tested during induction; testing rates considerably decreased thereafter (39 % during consolidation).
Conclusions: B-cell precursor ALL represents a clinical burden and impacts healthcare resources; MRD-positive patients have worse prognosis than MRD-negative patients. Efforts should be made to adhere to recommendations for MRD testing in clinical guidelines.

1. Introduction

Acute lymphoblastic leukemia (ALL) accounts for approximately 15–20 % of all adult acute leukemias [1]. The HAEMACARE Working Group estimated the overall crude incidence of ALL in Europe to be 1.28 per 100,000 individuals annually [2], qualifying this as a rare disease [3]. In that analysis the ALL definition comprised all cases of lymphoblastic lymphoma/acute [precursor cell] lymphatic leukemia, including B-cell, T-cell and not otherwise specified (NOS) subtypes irrespective of age. In contrast to most cancers, the incidence of ALL

Abbreviations: AE, adverse event; ALL, acute lymphoblastic leukemia; ALLIC-BFM, Acute Lymphoblastic Leukemia Inter-Continental Berlin-Frankfurt-Münster; AYA, adolescent and young adult; CI, confidence interval; CRh, Complete hematological response; ECOG, Eastern Cooperative Oncology Group; GMALL, German Modified Acute Lymphoblastic Leukemia; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; HCRU, healthcare resource utilization; HOVON, Hemato-Oncologie voor Volwassenen Nederland; HyperCVAD, Hyperfractionated Cyclophosphamide Vincristine, Adriamycin (doxorubicin), Dexamethasone; LOS, length of stay; MRD, minimal residual disease; NOS, not otherwise specified; NR, not reached; OS, overall survival; PCR, polymerase chain reaction; RFS, relapse-free survival; SD, standard deviation; SCT, stem cell transplantation

* Corresponding author at: Head of Hematology, AZ Delta, Wilgenstraat 2, B-8800, Roeselare, Belgium.
E-mail addresses: dries.deeren@azdelta.be (D. Deeren), Stefan.Balabanov@usz.ch (S. Balabanov), knickel@pharmerit.com (K. Nickel), cgiannop@amgen.com (C. Giannopoulou), sebgonza@amgen.com (S. Gonzalez-McQuire), luciek@amgen.com (L. Kutikova), wbouwmeester@pharmerit.com (W. Bouwmeester), spyridonidis@upatras.gr (A. Spyridonidis).

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peaks in children aged 0–14 years, with a crude incidence rate of 3.59 per 100,000 individuals in this age group [2]. B-cell precursor ALL is the most common type of ALL; the HAEMACARE Working Group estimated this to have an overall crude incidence of 0.08 per 100,000 individuals per year across age groups [2]. The definition used in that study included both B-cell precursor lymphoblastic lymphoma and B-cell precursor lymphoblastic leukemia. Overall, B-cell precursor ALL (1.28) had a higher crude incidence rate per 100,000 individuals than mature B-cell ALL (0.22; included Burkitt lymphoma, NOS and Burkitt cell leukemia) [2]. Intensive chemotherapy regimens alongside novel immunotherapies form the mainstay of treatment for ALL [4–6]. Nonetheless, treatment approaches are continuing to be optimized [7] and real-world data on how currently available regimens are used in clinical practice are lacking.

Although approximately 90 % of adults with ALL achieve complete remission, most of them relapse and die of their disease [8]. Nonetheless, overall survival (OS) rates have improved for adults with mature B-cell ALL [7], with much of this improvement linked to the adoption of pediatric-inspired regimens [4]. In contrast however, survival remains poor for adults with B-cell precursor ALL [9], especially for those in whom minimal residual disease (MRD) is not eradicated during front-line treatment. MRD is an established prognostic factor in ALL, which is defined as the presence of leukemic cells at levels below the detection threshold using conventional morphologic methods [10,11]. MRD positivity is the most important risk factor for hematologic relapse [6,12], with MRD-positive (MRD+) patients having worse prognosis than MRD-negative (MRD-) patients [10,13]. MRD status also impacts on disease management. For example, MRD positivity is a marker for high-risk disease and so is used to inform treatment decision-making [4,14]. A key therapeutic goal in ALL is the achievement of MRD- status [3] early in treatment. Flow cytometry and polymerase chain reaction (PCR) can identify trace levels of malignant cell biomarkers in bone marrow samples from patients achieving a hematological complete response (CRh) and so are commonly used to evaluate MRD status. Although European guidelines recommend MRD testing in patients with ALL during their first CRh [3], it is unclear whether this occurs in clinical practice. There is, therefore, a need to understand how ALL is managed and whether MRD positivity impacts on patient management and outcomes in routine clinical practice.

The overall objective of this descriptive study was to assess the burden associated with B-cell precursor ALL in terms of clinical outcomes and healthcare resource utilization (HCRU) in routine clinical practice, as well as to collect real-world data on MRD testing.

2. Methods

2.1. Study design and patients

To fill the existing data gap in current literature, this study was conducted in Belgium, Greece and Switzerland. A sample of physicians who were personally responsible for initiating anti-tumor treatment in patients with B-cell precursor ALL were invited to participate. Overall, approximately 70 %, 33 % and 85 % of the 367, 180 and 150 Swiss, Greek and Belgian hematologists in the database were invited, respectively. Those who consented to participate in real-world research conducted a retrospective medical chart review of eligible patients, extracting relevant data from their charts at their practice or study site in 2018. In total, 22 physicians were included, 15 from Greece, 4 from Belgium and 3 from Switzerland. Most of the 22 physicians included were hematologists (82 %); 9% were oncologists and 9% were hematologist-oncologists, and most were based in academic centers (68 %). The physicians had treated a median of 10 (range: 3–50) ALL patients in the past year and had a median of 13 (range: 5–34) years' experience in managing ALL.

Eligible patients were aged ≥18 years and newly diagnosed with B-cell precursor ALL (pre-B-cell, common B-cell or pro B-cell subtypes) between January 1, 2011 and December 31, 2017. Patients also needed to have received ≥1 MRD test during front-line induction or consolidation treatment. Inclusion started with the most recently diagnosed patients to capture the advances in the disease management patterns in recent years. This study was approved by the Freiburger Ethikkommission international, Freiburg, Germany in December 2017. After approval, patient-level data were abstracted between June and November 2018.

Patients were observed from diagnosis until death, last available record, or end of observation period, whichever occurred first. Data on disease management, MRD status and testing patterns were collected over the course of front-line treatment.

2.2. Variables analyzed

Patient characteristics are reported at ALL diagnosis and MRD status at first available test result; characteristics were assessed overall and stratified by MRD status and country. Patients were classified as MRD-, if they tested negative in any of the tests during front-line treatment, MRD unknown (those in whom an MRD test was performed but the test result was unknown) and MRD+. The incidence of selected comorbidities was also assessed (cardiovascular disease, renal disease, chronic pulmonary disease, and diabetes).

Front-line treatment patterns (e.g. treatment protocols, stem cell transplantation [SCT], maintenance treatment, duration, etc) were reported overall and stratified by MRD status and country. Front-line treatment was defined as first-line ALL treatment until either end of treatment, death or relapse (whichever occurred first). Front-line treatment could include pre-induction and induction with chemotherapy only, or followed by allogeneic/autologous SCT and consolidation, and maintenance therapy. Treatment duration was defined as the time from front-line therapy initiation until the end of maintenance therapy (for patients receiving maintenance therapy), front-line therapy termination, start of SCT (for patients receiving SCT), relapse or death. Information regarding the treatment protocols mentioned here is available at http://www.hovon.nl/general/welcome.html and in relevant guidelines [3,11]. Treatment duration was defined as the time from front-line therapy initiation until the end of maintenance therapy (for patients receiving maintenance therapy), front-line therapy termination, start of SCT (for patients receiving SCT), relapse or death.

Measures of HCRU included all hospitalizations (irrespective of reason) and length of stay (LOS). As hospitalizations could occur multiple times for each patient, mean LOS was calculated based on the sum of all the LOS's (total LOS) for all hospitalizations for each patient. LOS data were analyzed overall and by country. HCRU was investigated from first MRD test until SCT (for patients receiving SCT), start of maintenance therapy (for patients with maintenance therapy but no SCT) or front-line therapy termination (all other patients). These timeframes were chosen to reflect the real-world ALL disease management options in the front line. To permit assessment of the impact of MRD on outcomes, the start of follow-up for the HCRU analyses was the first MRD test. To account for different follow-up times, the number of hospital admissions and the sum of days hospitalized were divided by the HCRU follow-up duration for each patient. This resulted in a standardized number of hospitalizations and length of hospital stay per patient and per month of HCRU follow-up.

Clinical outcomes included the proportion of patients achieving a CRh during front-line treatment, relapse-free survival (RFS) and OS. Data were analyzed overall and stratified by MRD status. Data on clinical outcomes were collected over the entire follow-up period and median durations of RFS and OS estimated by Kaplan-Meier methodology.

MRD testing patterns were reported overall and stratified by country. Details of the methods used for testing (i.e. flow cytometry or PCR) were also included.

Table 1
Patient and disease characteristics at diagnosis by MRD status (at first test).

Variable	N in analysis	ALL (N = 82)	N in MRD analysis	MRD- ALL (n = 50)	MRD+ ALL (n = 17)
Age, years – median (range)	82	44 (19–80)	67	35.5 (19–73)	43 (20–75)
AYA population (15–39 years), n (%)		35 (42.7)	34	29 (58.0)	5 (29.4)
Country, n (%)	82		67		
Belgium		23 (28.0)		10 (20.0)	0 (0.0)
Greece		52 (63.4)		33 (66.0)	17 (100.0)
Switzerland		7 (8.5)		7 (14.0)	0 (0.0)
MRD status, n (%)	82		67		
MRD-		50 (61.0)		50 (100)	–
MRD+		17 (20.7)		–	17 (100)
No test result[a]		15 (18.3)		–	–
ECOG status, n (%)	80		67		
0		37 (46.3)		28 (56.0)	8 (47.1)
1		28 (35.0)		16 (32.0)	3 (17.6)
2		12 (15.0)		5 (10.0)	4 (23.5)
3		3 (3.8)		1 (2.0)	2 (11.8)
Philadelphia chromosome positive, n (%)	82	19 (23.2)	67	8 (16.0)	7 (41.2)
CNS involvement, n (%)	82		67		
Yes		3 (3.7)		2 (4.0)	1 (5.9)
No		72 (87.8)		48 (96.0)	16 (94.1)
Not tested/result unknown		7 (8.5)		0 (0)	0 (0)
Comorbities,[b] n (%)	82		67		
Moderate/severe cardiovascular disease		8 (9.8)		4 (8.0)	1 (5.9)
Renal disease		5 (6.1)		0 (0.0)	0 (0.0)
Chronic pulmonary disease		8 (9.8)		3 (6.0)	3 (17.6)
Diabetes with chronic complications/end-stage disease		4 (4.9)		2 (4.0)	0 (0.0)
None of the above		62 (75.6)		44 (88.0)	12 (70.6)
Unknown		1 (1.2)		0 (0.0)	0 (0.0)
Leukocyte count, 10^9/L – median (range)	68	22 (1–50)	65	20 (1–49)	30 (4–42)
Bone marrow blast cell count, % – median (range)	69	75 (20–100)	66	80 (20–100)	67 (25–100)
Length of follow-up – median (range), months	82	15.2 (2.4–87.0)	67	23.6 (2.4–87.0)	14.0 (12.6–34.9)

[a] MRD tests were performed in 15 patients, but no result was recorded.
[b] Comorbidity categories are not mutually exclusive.

All analyses were descriptive (no statistical tests were conducted to test for differences). All analyses were performed in R version 3.5.1 (2018-07-02; "Survival" R-package https://cran.r-project.org/web/packages/survival/survival.pdf).

3. Results

3.1. Patients

Overall, 82 patients were included in the study (63 %, 28 % and 8% were from Greece, Belgium and Switzerland, respectively) and the actual median follow-up was 15.2 (range: 2–87) months (Table 1). The patients' median age was 44 (range: 19–80) years, with Belgian patients appearing older at diagnosis (median age: 57 [range: 20–80] years) than Greek patients (median age: 37 [range: 19–75] years) (Table A1). Overall, 81 % of patients had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1; proportions were 70 % and 83 % in Belgium and Greece, respectively. In total, 23 % of patients had positive Philadelphia chromosome status; with similar proportions seen in Greek and Belgian patients (25 % and 26 %, respectively). Overall, 23 % of patients had at least one of the assessed comorbidities at diagnosis, with more Belgian patients (43 %) appearing to have comorbidities than those from Greece (17 %). There were too few patients from Switzerland (n = 7) to draw comparisons with this country.

Most patients in this study (61 %) achieved MRD- status during front-line treatment. Patients that remained MRD+ during front-line treatment had a median age of 43 (range: 20–75) years at diagnosis (MRD-: median of 35.5 [range: 19–73] years) and 41 % of the MRD+ group had positive Philadelphia chromosome status (MRD-: 16 %). Of the 35 patients aged < 40 years in our study, 29 were MRD- and 28 were from Greece; 23 patients were both Greek and MRD- (total number of MRD- Greek patients n = 33).

3.2. Front-line treatment patterns

Overall, the most commonly used front-line treatments were HyperCVAD (32 %) and HOVON (26 %) protocols; the rest of the patients (42 %) received other protocols, including GMALL, GRAALL and ALLIC-BFM (Table 2). Nearly all of the Belgian patients (91 %) were treated following HOVON protocols, whereas the most common protocols in Greece were HyperCVAD (50 %) and GMALL (21 %) (Table A2). All the Swiss patients (n = 7) received front-line treatment following the GRAALL protocol. Overall, the median duration of front-line treatment was 6.9 (range: 1.0–43.5) months. In total, 22 % of patients received SCT (13 % allogeneic, 2% autologous, 6% unknown), with fewer Greek than Belgian patients receiving SCT (17 % and 35 %, respectively). Across the study, 41 % of patients received maintenance therapy (5 patients received both SCT and maintenance therapy and so are included in both percentages; 4/5 patients received maintenance therapy prior to receiving SCT). More Greek than Belgian patients received maintenance treatment (48 % and 17 %, respectively). In total, 29 % of patients did not receive SCT or maintenance therapy due to disease progression (50 %), death (29 %) or adverse events (25 %).

Patients with MRD- status appeared to have a longer median duration of treatment (8.8 and 3.2 months), to be more likely to receive maintenance treatment (54 % and 29 %) and to be less likely to discontinue treatment prior to initiation of SCT or maintenance therapy (14 % and 41 %) than those with MRD+ status (Table 2).

3.3. HCRU

The follow-up for HCRU (from first MRD test until SCT, start of maintenance therapy or front-line therapy termination) was a median of 5.0 (range: 0–20.8) months for the 73 patients who had an MRD testing date (and no missing end date). Overall, 56/73 patients (77 %) were hospitalized; these 56 patients were hospitalized a mean of 1.1

Table 2
Front-line treatment patterns.

Variable	N in analysis, all/MRD	ALL (N = 82)	MRD- ALL (n = 50)	MRD + ALL (n = 17)
Main treatment protocol used,[a] n (%)	82/67			
HyperCVAD		26 (31.7)	18 (36.0)	7 (41.2)
HOVON		21 (25.6)	10 (20.0)	0 (0.0)
GMALL		11 (13.4)	5 (10.0)	5 (29.4)
GRAALL		9 (11.0)	9 (18.0)	0 (0.0)
ALLIC-BFM		5 (6.1)	4 (8.0)	1 (5.9)
Other protocol		10 (12.2)	4 (8.0)	4 (23.5)
Duration of treatment,[b] months – median (range)	79/65	6.9 (1,0–43.5)	8.8 (1.4–43.5)	3.3 (1.9–14.8)
Received SCT,[c] n (%)	82/67	18 (22.0)	12 (24.0)	4 (23.5)
Received maintenance therapy,[c] n (%)	82/67	34 (41.5)	27 (54.0)	5 (29.4)
Time to SCT from front-line therapy initiation, months – median (range)	18/16	6.6 (3.2–10.1)	7.4 (3.2–10.1)	6.1 (4.0–6.1)
Discontinued treatment prior to SCT or maintenance, n (%)	82/67	24 (29.3)	7 (14.0)	7 (41.2)
Reason for discontinuation, n (%)	24/14			
Disease progression		12 (50.0)	2 (28.6)	5 (71.4)
Death		7 (29.2)	3 (42.9)	2 (28.6)
AE complications		6 (25.0)	2 (28.6)	1 (14.3)
Refusal		2 (8.3)	0 (0.0)	0 (0.0)
Other		12 (50.0)	2 (28.6)	5 (71.4)

[a] Used protocol versions included: ALLIC-BFM Version: 1/2/2000; GMALL Version: a/2003; GRAALL Version: 2003/2005/2014; HOVON Version: 71 + imatinib/70/71/ALL-6A + imatinib/ALL-6B standard induction, consolidation and +/- SCT, and/or maintenance treatment/induction ALL; HyperCVAD Version: 1/2001/2004/2010/2011/A/MD ANDERSON 2010/unknown.
[b] Includes maintenance and SCT (3 Greek patients had ongoing maintenance treatment at the end of the study and were excluded from the analysis).
[c] Five patients received SCT and maintenance therapy (4 patients received maintenance therapy before SCT, likely while they were awaiting SCT).

times per month (standard deviation [SD]: 1.4). The standardized mean LOS was 12.8 days (SD: 8.8); median LOS was 10.1 (range: 0.7–30.4) days. Greek patients appeared to have more hospitalizations/month (standardized mean: 1.06 and 0.88, respectively) and longer LOS per patient per month (standardized mean: 14.0 and 9.5 days, respectively) than Belgian patients. In general, both the standardized mean number of hospitalizations (range: 0.1–10.1) and the total LOS (range: 0.7–30.4 days) varied considerably.

3.4. Clinical outcomes

Overall, a CRh occurred in 66/82 patients (80 %) during front-line treatment. For the total population, median RFS from CRh (n = 62) was 32.7 months (95 % confidence interval [CI]: 21.1–not reached [NR]) and 30 patients (48 %) had an RFS event (hematological relapse: n = 19; death: n = 11) (Fig. 1A). The RFS curve plateaued at 35 % from 34 months after CRh until the end of follow-up. Median RFS was longer in patients who tested MRD- in any test during front-line treatment (n = 46) than in those who remained MRD+ (n = 13; 33.3 months [95 % CI: 24.3–NR] and 11.7 months [95 % CI: 2.8–NR], respectively) (Fig. 1B). The RFS curves plateaued at 38 % after 34 months and 30 % after 15 months for MRD- and MRD+ patients, respectively.

For the total population, median OS from diagnosis was 28.9 months (95 % CI: 23.4–NR) and 35 patients (43 %) died during follow-up (Fig. 2A). The OS curve plateaued at 39 % from 39 months after diagnosis until the end of follow-up. Overall, 71 %, 60 % and 39 % of patients were alive at 1, 2 and 5 years, respectively. Of those with known MRD status (n = 67), 28 patients (42 %) died during follow-up; 17/50 (34 %) of MRD- and 11/17 (65 %) of MRD+ patients. Median OS was NR (95 % CI: 28.9–NR) in MRD- patients and the associated OS curve plateaued at 50.1 % from 39 months after diagnosis until the end of follow-up (Fig. 2B). Median OS was 15.3 months (95 % CI: 11–NR) in MRD+ patients. With respect to those with MRD- status, 83 %, 74 % and 50 % were alive at 1, 2 and 5 years, respectively. Survival rates at 1 and 2 years for the MRD+ group were 59 % and 33 %, respectively.

3.5. MRD testing patterns

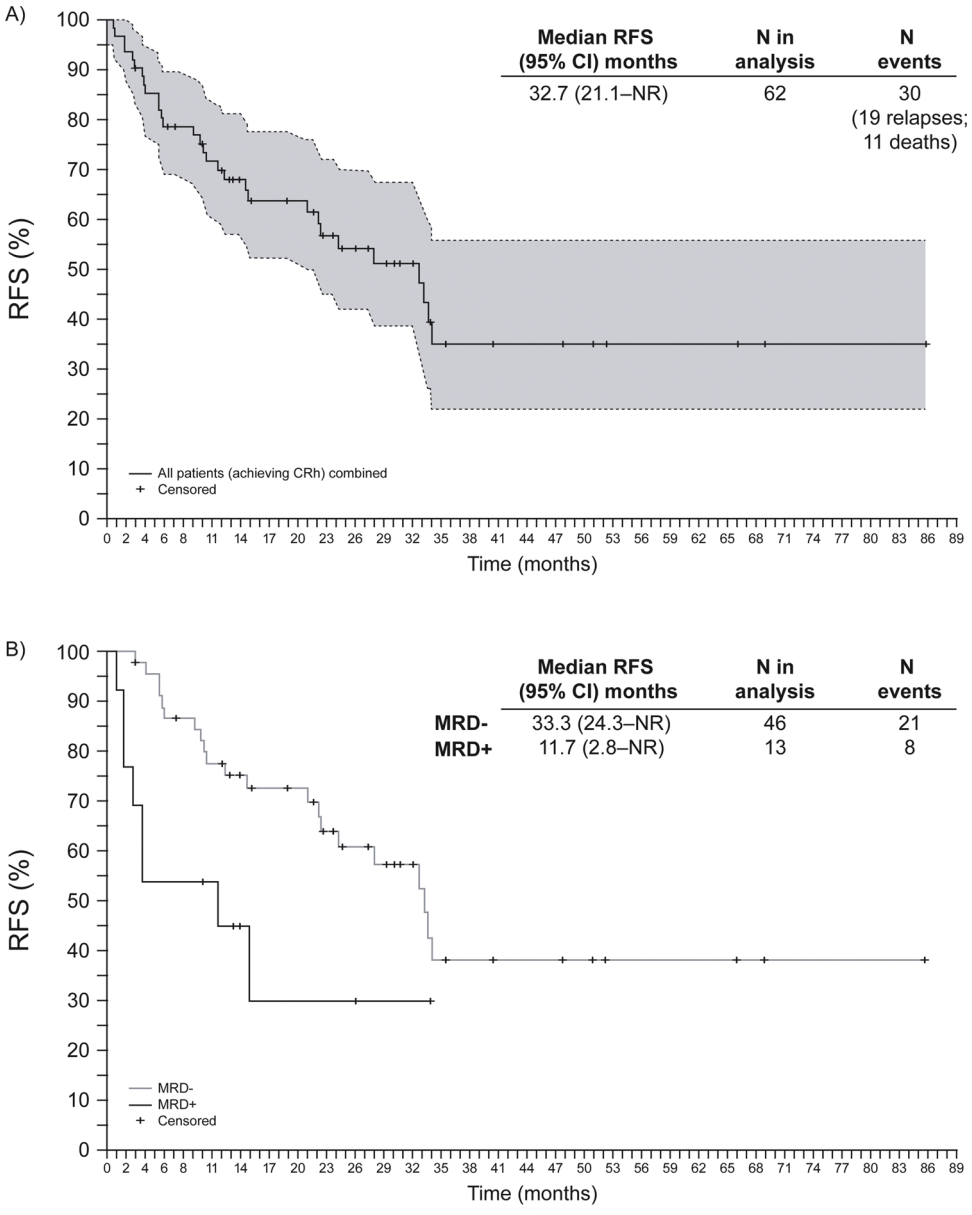
Most patients (88 %) had their MRD status tested during induction; testing rates considerably decreased thereafter, with only 39 % of patients being MRD tested during consolidation (Table 3). Similar results were seen by country; 70 % and 96 % of Belgian and Greek patients were tested during induction and 39 % and 37 % were tested during consolidation treatment (Table A2). For the 13 patients receiving SCT who had information available, 85 % were MRD tested after SCT. For those receiving maintenance treatment who had information available (n = 29), 79 % were MRD tested during this stage of treatment.

Overall, patients received a mean of 2.3 (SD: 1.7) MRD tests during front-line therapy prior to SCT/maintenance treatment (Table 3); similar results were seen in Belgium (2.0 [SD: 1.6]) and Greece (2.3 [SD: 1.9]) (Table A2). In patients with ≥1 MRD test (and a date of test available; n = 73), their first test occurred a median of 1.2 months after initiation of front-line treatment. In those patients with ≥2 test results (and a date of test available; n = 41), the second test occurred a median of 1.2 months later. In Belgium, the first MRD test occurred earlier (median 1.2 and 1.4 months after front-line treatment initiation) and the second MRD test followed later (median 1.6 and 1.1 months after the first test) than in Greece. Overall, the frequency of MRD testing varied over time with a peak at approximately 5 weeks after initiation of front-line treatment (Fig. 3) (at weeks 5 and 9 in Greece; Figure A1B). MRD testing continued over the course of the treatment (the last test was conducted at 92 weeks post initiation), although the number of tests reduced over time. In general, fewer tests were conducted per week after week 10 (< 7 MRD tests performed per week after this point). In Belgium, the number of MRD tests performed was too low to draw any conclusions regarding any change in frequency of testing over time (Fig. A1A).

Overall, flow cytometry was used for MRD testing in 60 % of tests and PCR was used in 26 % (Table 3). PCR was the most common MRD testing method in Belgium (67 %), whereas flow cytometry-based assays were most commonly used in Greece (72 %). Across the study, the limit of sensitivity for determining MRD negativity was one leukemic blast in 10^4 cells (1×10^4) in 71 % of tests.

4. Discussion

This medical chart review provides real-world data on treatment, MRD testing patterns and clinical/economic outcomes for adult patients (≥18 years old) receiving front-line treatment for B-cell precursor ALL



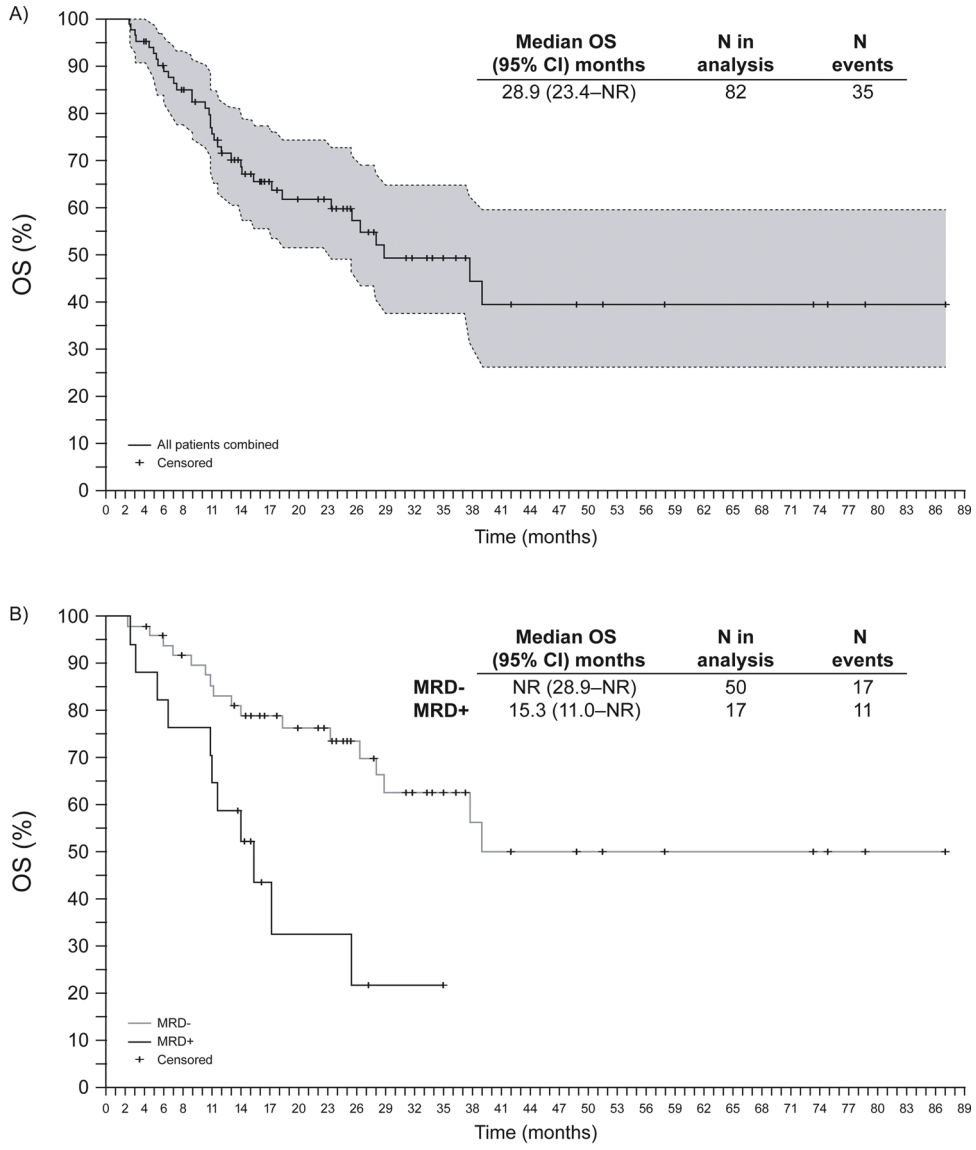
[a]Patients with unknown MRD status were not included in the analysis. The shaded areas represent the associated 95% CI

Fig. 1. RFS from CRh (A) for all patients with ALL and (B) by MRD status[a].

in Belgium, Greece and Switzerland. Our results highlight that ALL is an aggressive disease that is associated with poor prognosis and considerable clinical and economic burden. Our findings also support previous observations that MRD+ patients have worse prognosis than MRD- patients [10] and highlight the clinical relevance of testing MRD status outside of a clinical trial setting.

Although HCRU during front-line treatment varied considerably between patients in our study, in general, a substantial amount of HCRU was observed. Overall, 76 % of ALL patients were hospitalized, with patients incurring 1 hospitalization/month on average and a mean length of hospital stay of 13 days (median LOS was 10.1 days). Additional hospitalizations may have occurred outside of the HCRU hospitalization period, which spanned the time from first MRD test until SCT, start of maintenance therapy or front-line therapy termination/death. Likewise, as this study included those who had been recently diagnosed with ALL, follow-up was short for some patients and any hospitalization may have occurred after data abstraction. This may mean that the amount of HCRU associated with ALL could have been underestimated in this study.

Overall, median OS from diagnosis for the patients included in this study was approximately 2.5 years. The similarity in shape of the OS and RFS Kaplan-Meier curves, indicates a high correlation between OS and RFS in ALL, with patients having a high risk of death after relapse. This highlights the need for patients to receive effective front-line ALL treatment that focuses on preventing relapse. A plateau in OS occurred in approximately 39 % of patients from 39 months after diagnosis until the end of follow-up, suggesting possible disease cure in these patients. This plateau appeared to mainly be driven by MRD- patients, which reinforces the importance of achieving MRD negativity as early as possible during treatment. Although our real-world data support previous observations of the poor prognosis associated with MRD+ compared with MRD- status, comparisons between these groups need to be treated with caution due to the limited sample size. Furthermore, it appeared that some prognostic variables at diagnosis (e.g. age, Philadelphia chromosome status, etc) were correlated with MRD status at first MRD test, with MRD+ patients generally showing more risk



[a]Patients with unknown MRD status are not included in the analysis. The shaded areas represent the associated 95% CI

Fig. 2. OS (A) All patients with ALL and (B) by MRD status[a].

factors at diagnosis than MRD- patients. However, it should be noted that the OS and RFS analyses are presented without censoring patients at SCT because censoring excludes patients from the analyses and so further reduces the limited sample size of some groups.

In this real-world study, MRD testing was most frequent during induction and then generally declined over the course of treatment. The highest number of MRD tests per week conducted was approximately 5 weeks after front-line therapy initiation, which is a timepoint often used for treatment decision-making. This is especially true for newer protocols such as GRAALL 2014 (EUDRA CT number: 2014-002146-44), which uses MRD status to define disease risk and subsequent treatment. The timing of the initial MRD test was similar to observations in a previous study that reported a peak in MRD testing 4 weeks after the start of induction therapy [15]. In general, fewer MRD test results were reported 16 weeks after front-line treatment initiation in our study, despite the fact that MRD results around this time are deemed clinically more relevant for long-term prognosis than results from earlier timepoints [16–21]. This could be because patients died, were lost to follow-up or relapsed and initiated second-line treatment. It could also be due to the use of older treatment protocols in which MRD testing was not mandatory at week 16. For instance, in Belgium nearly all patients were treated using HOVON protocols including older regimens such as HOVON-70. MRD testing is also a burdensome procedure, which may mean physicians are reluctant to continue testing. The general lack of testing beyond induction is a concern given the prognostic impact and therapeutic consequences of MRD status [10,13]; it is important to continue to evaluate MRD throughout treatment to ensure appropriate patient management. In-line with this, current European Society of Medical Oncology ALL guidelines state that molecular remission is the most relevant independent prognostic factor for disease-free survival and OS in patients with ALL [3]. Furthermore, they suggest that as MRD is a well-established risk factor, quantification of this should be done whenever possible for all patients.

Overall, and in Greece in particular, flow-cytometry-based methods were most commonly used to test MRD status in our study. As flow cytometry methods are not standardized, it can be difficult to compare flow cytometry results between sites/countries.

Some between- and within-country differences in patient characteristics and treatment patterns were observed in our study, suggesting a lack of consensus on optimal ALL management. For example,

Table 3
MRD testing patterns.

Variable	N in analysis	ALL
Patients being MRD tested during front-line therapy, n (%)	82[a]	81[b] (98.8)
Pre-induction[c]	82[a]	11 (13.4)
Induction[c]	82[a]	72 (87.8)
Consolidation[c]	82[a]	32 (39.0)
Other[c]	82[a]	14 (17.1)
During hospitalization for SCT[c]	13	5 (38.5)
Post-SCT[c,d]	13	11 (84.6)
During maintenance[c,e]	29	23 (79.3)
Number of MRD tests per patient during front-line therapy prior to SCT or maintenance – mean (SD) median (range)	82[a]	2.3 (1.7) 2 (0–9)
Pre-induction – mean (SD) median (range)	82[a]	0.1 (0.3) 0 (0–1)
Induction – mean (SD) median (range)	82[a]	1.3 (0.9) 1 (0–5)
Consolidation – mean (SD) median (range)	82[a]	0.6 (0.9) 0 (0–4)
Other – mean (SD) median (range)	82[a]	0.3 (0.7) 0 (0–5)
Method used to test MRD status, n (%)	217	
Flow cytometry		130 (59.9)
PCR		57 (26.3)
Time from start of front-line therapy to first MRD test, months – median (range)	73	1.2 (0–11.7)
Time from first to second MRD test, months – median (range)	41	1.2 (0–10.8)

[a] Includes patients who were MRD tested but for whom no MRD status result was available.
[b] One patient was recorded as being MRD tested during front-line therapy, but the number of MRD tests performed was documented as 0, therefore, they were assumed to not have been MRD tested for the purpose of this analysis; Nearly 100 % of patients had an MRD test result during front-line therapy, as having at least 1 MRD test in front line was a requirement for inclusion in the study.
[c] Patients could be MRD tested during multiple stages of treatment.
[d] Includes those patients who received SCT (with or without maintenance) who had MRD data available post SCT.
[e] Includes only those patients who received maintenance and no SCT.

compared with Greece, patients from Belgium appeared to have more severe disease (i.e. they were older, had more comorbidities and a higher bone marrow blast cell count) and had higher rates of SCT. This may be a chance finding or because patients from Belgium were clustered around centers of excellence in one area, which may treat patients with more severe disease (who are more likely to receive SCT than those with standard risks) [4]. Conversely, participating medical centers in Greece covered a wider geographical area and so may have seen a more varied patient caseload. There is often a preference for the use of certain ALL protocols within a given country and our results are supportive of this. For instance, there was a much greater use of HOVON protocols in Belgium than in Greece, probably due to the participation of many of the Belgian physicians in the HOVON study group.

Overall, the findings of this study were similar to those reported previously with respect to patient baseline characteristics, MRD testing timepoints and outcomes [10,13,15,22]. Any observed differences may

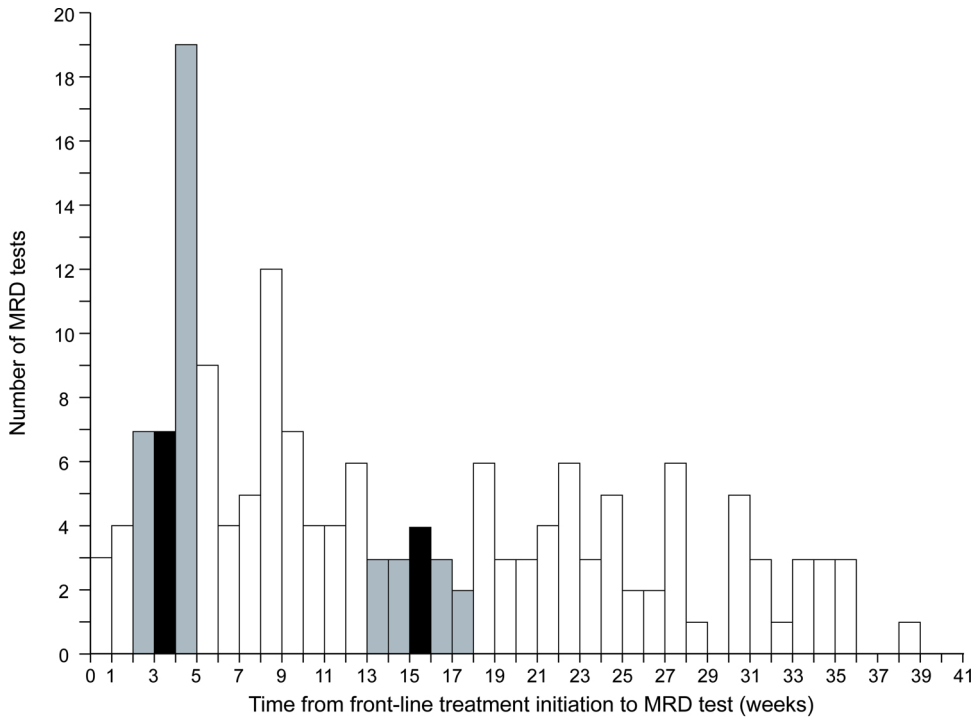


Fig. 3. MRD testing patterns during front-line ALL treatment.

be due to differences in study design (e.g. one previous study was based on the results of a physician survey that included estimated patient management data [15], one included a variety of ALL patients [10] and another only included responders [22]). In contrast to these other publications, the current study purely reports retrospective data on how patients were managed in routine clinical practice in Belgium, Greece and Switzerland.

A strength of this study is that it provides real-world data on the management and outcomes of adults with B-cell precursor ALL from three European countries, which are rarely studied. The overall sample size in this study (n = 82) was relatively large for this rare disease and is larger than in many recent observational studies in adult ALL [23–28]. However, it was small for some subgroups (e.g. MRD+ patients). The relatively high number of patients who were MRD tested but had no available test result (18 %) further reduced sample size in the MRD analyses. There are several possible explanations for these missing results. For example, the results may have been stored within the HOVON study group, who conducted the tests for the Belgian physicians (13/15 missing results were from Belgium). In the HOVON studies, MRD testing was part of the protocol, but since this was considered experimental at that point, the results were not communicated to the investigators. In addition, it is common practice to test MRD status in SCT-eligible patients. The patients without a test result were older (median age: 64 [range 39–80] years), probably had a worse prognosis (a low proportion [3/15: 20 %] achieved a CRh) and were unlikely to be eligible for SCT (only 2/15 [13 %] received SCT), so their test results may have been viewed as unimportant. The time burden on physicians required to complete the electronic case report forms may also have been a factor. Nonetheless, the fact that all 82 patients received an MRD test but for 18 %, their results were not known suggests a potential educational need for physicians regarding the importance and prognostic impact of MRD status. Alternatively, this may be a historical artefact and practice may have changed since the time these patients were managed.

In summary, these real-world data are supportive of B-cell precursor ALL being an aggressive disease associated with considerable clinical burden, which also impacts on HCRU. The poorer prognosis associated with MRD+ highlights the clinical relevance of MRD testing outside of a clinical trial setting and supports achievement of MRD- status as a key treatment goal for ALL patients undergoing front-line treatment. In this study MRD testing was not performed in-line with current guidelines (GRALL [29]; HOVON [30], HYPERCVAD [31]) and so there is room for improvement with respect to this in clinical practice. Additional testing of MRD status beyond the induction stage and regularly throughout a patient's treatment journey may help improve outcomes by permitting appropriate patient management based on MRD status. Furthermore, front-line treatment patterns varied overall and between countries in this study suggesting a lack of consensus on optimal management of this disease. As there is a high risk of death following relapse in ALL, it is important that the most effective available therapies are used first in this aggressive disease to limit the risk of relapse.

Data availability

The data that have been used in these analyses are confidential.

Author contributions

DD, SB and AS contributed to the interpretation of study data. KN and WB contributed to the study design and the analysis and interpretation of study data. CG, SGM and LK contributed to the study design and interpretation of the data. All authors were involved in drafting the paper and/or revising it critically for important intellectual content, approved the final draft and agreed to be accountable for all aspects of the work.

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